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None

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UK CL (Edition K) **C2C CLF CLJ**
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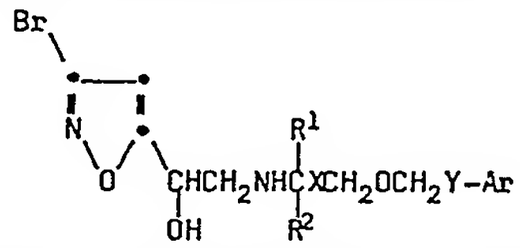
(54) 1-(3-Bromoisoxazol-5-yl)-2-aminoethanol derivatives

(57) Ethanolamine derivatives are disclosed of formula (I)



(I)

and physiologically acceptable salts thereof, wherein R^1 and R^2 represent hydrogen or a C_{1-3}alkyl group with the proviso that the sum total of carbon atoms in R^1 and R^2 is not more than 4; X represents a bond or a C_{1-7}alkylene, C_{2-7}alkenylene or C_{2-7}alkynylene group and Y represents a bond or a C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene group with the proviso that the sum total of carbon atoms in X and Y is not more than 10; and Ar represents an optionally substituted phenyl or pyridyl.

The compounds (I) have *stimulant action at* β_2*-adrenoreceptors* and may be used in the treatment of conditions associated with reversible airways obstruction, such as asthma and bronchitis , and in the treatment of inflammatory and allergic skin diseases, congestive heart failure, depression, premature labour, glaucoma and gastric and peptic ulceration. Pharmeceutical compositions containing the compounds (I) as active ingredient are disclosed and also processes for the production of the compounds (I).

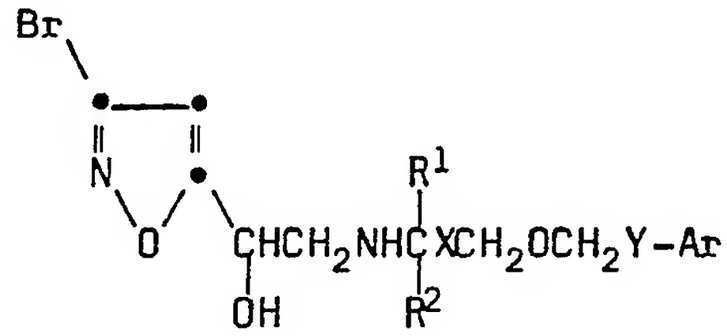
The claims were filed later than the filing date within the period prescribed by Rule 25(1) of the Patents Rules 1982.

GB 2 230 523 A

CHEMICAL COMPOUNDS

This invention relates to ethanolamine derivatives having a stimulant action at β_2-adrenoreceptors, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

Thus the present invention provides compounds of general formula (I)



(I)

and physiologically acceptable salts thereof, wherein

R^1 and R^2 each independently represent a hydrogen atom or a C_{1-3}alkyl group with the proviso that the sum total of carbon atoms in R^1 and R^2 is not more than 4;

X represents a bond or a C_{1-7}alkylene, C_{2-7}alkenylene or C_{2-7}alkynylene group and Y represents a bond or a C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene group with the proviso that the sum total of carbon atoms in X and Y is not more than 10;

Ar represents a monocyclic aryl group selected from unsubstituted or substituted phenyl or unsubstituted or substituted pyridyl.

When Ar represents a substituted phenyl group, this may be substituted by one or more substituents selected from halogen atoms, C_{1-4}alkyl, C_{1-4}alkoxy or hydroxy groups, or by an alkylenedioxy group of formula $-O(CH_2)_pO-$ where p is 1 or 2.

When Ar represents a substituted pyridyl group, this may be substituted by one or more substituents selected from halogen atoms, C_{1-4}alkyl, C_{1-4}alkoxy or hydroxy groups.

It will be appreciated that the compounds of general formula (I) possess at least one asymmetric carbon atom. The compounds according to the invention thus include all enantiomers, diastereomers and mixtures thereof, including racemates. Compounds in which the carbon atom in the -CH(OH)- group is in the R configuration are preferred.

As used herein the term alkenylene includes both cis and trans structures.

Conveniently R^1 and R^2 each represent a hydrogen atom or a methyl group. In particular R^1 and R^2 conveniently both represent hydrogen atoms.

The chain X may be for example $-(CH_2)_2$, $-(CH_2)_3-$, $(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_6-$, $(CH_2)_2CH=CH-$, $-(CH_2)_2C\equiv C-$, $-CH=CHCH_2-$, $-CH=CH(CH_2)_2-$ or $-CH_2C\equiv CCH_2-$.

The chain Y may be for example a bond, $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-(CH_2)_5-$, $-CH_2CH=CH-$ or $-CH_2C\equiv C-$.

Preferably the sum total of carbon atoms in chains X and Y is 4 to 10 inclusive.

When Ar represents a pyridyl group, this may be attached to the rest of the molecule at either the 2-, 3- or 4-position. When the pyridyl group is substituted, the substituent(s) may be at the 2-, 3-, 4-, 5- or 6-position(s) in the ring.

When Ar represents a substituted phenyl group, the substituents may be present at the 2-, 3-, 4-, 5- or 6-position(s) on the phenyl ring.

Examples of substituents which may be present on the aromatic ring Ar include chlorine, bromine, fluorine, iodine atoms, methyl, ethyl, methoxy, ethoxy and hydroxy groups.

Conveniently Ar represents an unsubstituted phenyl or pyridyl group.

Preferred compounds according to the invention are those in which R^1 and R^2 each represent a hydrogen atom and Ar represents an unsubstituted phenyl or pyridyl group.

Compounds according to the invention wherein R^1 and R^2 each represent a hydrogen atom and the sum total of carbon atoms in the chains X and Y is 4, 5, 6, 7, 8, 9 or 10 are also preferred.

Preferred compounds according to the invention include :

3-Bromo-α-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-5-isoxazolemethanol,

3-Bromo-α-[[[6-[[6-(2-pyridinyl)hexyl]oxy]hexyl]amino]methyl]-5-isoxazolemethanol,

and their physiologically acceptable salts.

Suitable physiologically acceptable salts of the compounds of general formula (I) include acid addition salts derived from inorganic and organic acids, such as hydrochlorides, hydrobromides, sulphates, phosphates, maleates, tartrates, citrates, benzoates, 4-methoxy-benzoates, 2- or 4-hydroxybenzoates, 4-chlorobenzoates, benzenesulphonates, p-toluenesulphonates, naphthalenesulphoates, methanesulphonates, sulphamates, ascorbates, salicylates, acetates, diphenylacetates, triphenylacetates, adipates, fumarates, succinates, lactates, glutarates, gluconates, tricarballylates, hydroxynaphthalenecarboxylates e.g. 1-hydroxy or 3-hydroxy-2-naphthalenecarboxylates, or oleates.

The compounds according to the invention have a stimulant action at β_2-adrenoreceptors. The stimulant action was demonstrated in the isolated trachea of the guinea-pig, where compounds were shown to cause relaxation of contractions induced by $PGF_2\alpha$ or electrical stimulation. A prolonged duration of action has also been observed.

The compounds according to the invention may be used in the therapy or prophylaxis of conditions susceptible to amelioration by a compound possessing selective stimulant action at β_2-adrenoreceptors, particularly of diseases associated with reversible airways obstruction such as asthma and chronic bronchitis. Further examples of conditions which may be alleviated by administration of a compound possessing selective β -stimulant activity are inflammatory and allergic skin diseases, congestive heart failure, depression, premature labour, glaucoma and conditions in which there is an advantage in lowering gastric acidity, particularly in gastric and peptic ulceration.

The invention thus further provides compounds of formula (I) and their physiologically acceptable salts for use as an active therapeutic agent in particular for the treatment of conditions subject to amelioration by a compound possessing selective stimulant action at β_2 -adrenoreceptors, for example diseases associated with reversible airways obstruction.

In a further or alternative aspect there is provided a method for the treatment of a disease associated with reversible airways

obstruction in a mammal including man comprising administration of an effective amount of a compound of formula (I) or a physiologically acceptable salt thereof.

There is also provided in a further or alternative aspect use of a compound of formula (I) or a physiologically acceptable salt thereof for the manufacture of a medicament for the treatment of a condition which may be ameliorated by a compound having selective β_2-adrenoreceptor stimulant activity.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established symptoms.

It is possible that a compound of the invention may be administered to a patient as the raw chemical, but it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention accordingly provides a pharmaceutical formulation comprising a compound of formula (I) or a physiologically acceptable salt thereof together with one or more physiologically acceptable carriers and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The compounds may be formulated in a form suitable for administration by inhalation or insufflation, or for oral, buccal, parenteral, topical (including nasal) or rectal administration. Administration by inhalation or insufflation is preferred.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs, with the use of a suitable propellant, such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetraflurorethane, carbon dioxide or other suitable gas, or from a nebuliser. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound an a

suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in for example capsules or cartridges of e.g. gelatin, or blister packs from which the powder may be administered with the aid of an inhaler or insufflator.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets, capsules, powders, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For buccal administration the composition may take the form of tablets, drops or lozenges formulated in the conventional manner.

The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulation for injection may be presented in unit dosage form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

For topical administration the pharmaceutical composition may take the form of ointments, lotions or creams formulated in a conventional manner, with for example an aqueous or oily base, generally with the addition of suitable thickening agents and/or solvents. For nasal application, the composition may take the form of a spray, formulated for example as an aqueous solution or suspension or as an aerosol with the use of a suitable propellant.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glyceride.

Where pharmaceutical compositions are described above for oral, buccal, rectal or topical administration, these may be presented in a conventional manner associated with controlled release forms.

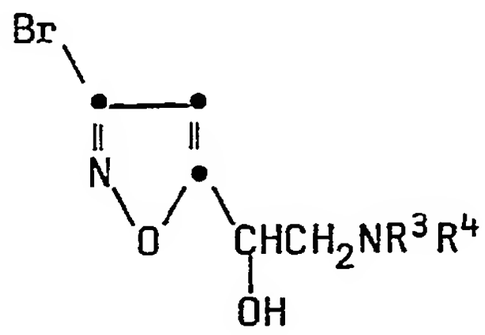
A proposed daily dosage of active compound for the treatment of man is 0.005mg to 100mg, which may be conveniently administered in one

or two doses. The precise dose employed will of course depend on the age and condition of the patient and on the route of administration. Thus a suitable dose for administration by inhalation is 0.005mg to 20mg, for oral administration is 0.02mg to 100mg, and for parenteral administration is 0.01mg to 2mg for administration by bolus injection and 0.01mg to 25mg for administration by infusion.

The compounds according to the invention may be prepared by any process known in the art for the preparation of compounds of analogous structure. In the following description, R^1, R^2, X, Y and Ar are as defined for general formula (I) unless otherwise specified.

In one general process, (A), a compound of general formula (I) may be prepared by alkylation. Conventional alkylation procedures may be used.

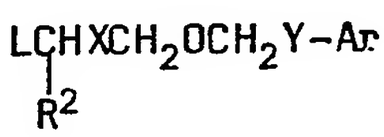
Thus, for example, in one alkylation process (a), a compound of general formula (I) in which R^1 is a hydrogen atom may be prepared by alkylation of an amine of general formula (II) :



(II)

(wherein R^3 represents a hydrogen atom or a protecting group and R^4 represents a hydrogen atom) followed by removal of any protecting groups where present.

The alkylation (a) may be effected using an alkylating agent of general formula (III) :



(III)

(wherein L is a leaving group, for example a halogen atom such as chlorine, bromine or iodine, or a hydrocarbylsulphonyloxy group such as methanesulphonyloxy or p-toluenesulphonyloxy).

The alkylation is preferably effected in the presence of a suitable acid scavenger, for example inorganic bases such as sodium or potassium carbonate, organic bases such as triethylamine,

diisopropylethylamine or pyridine, or alkylene oxides such as ethylene oxide or propylene oxide. The reaction is conveniently effected in a solvent such as acetonitrile or an ether e.g. tetrahydrofuran, a ketone e.g. butanone, a substituted amide e.g. dimethylformamide or a chlorinated hydrocarbon e.g. chloroform, at a temperature between ambient and the reflux temperature of the solvent.

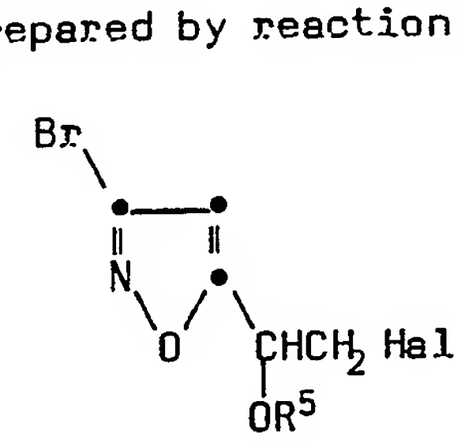
According to another example (b) of an alkylation process, a compound of general formula (I) in which R^1 represents a hydrogen atom may be prepared by alkylation of an amine of general formula (II), as previously defined except that R^3 is a hydrogen atom with a compound of general formula (IV) :

$$R^2COXCH_2OCH_2Y\text{-}Ar \qquad (IV)$$

in the presence of a reducing agent, followed when necessary by removal of any protecting groups.

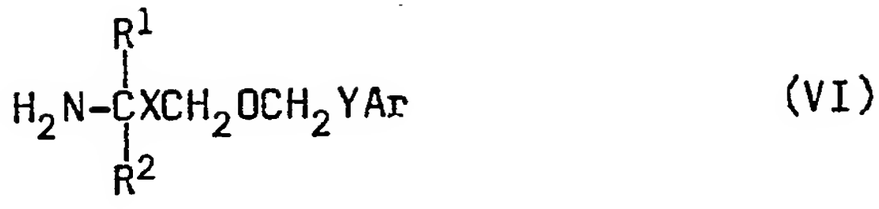
The reducing agent may be, for example, a hydride such as diborane or a metal hydride such as sodium borohydride, sodium cyanoborohydride or lithium aluminium hydride. Suitable solvents for the reaction with these reducing agents will depend on the particular hydride used, but will include alcohols such as methanol or ethanol, or ethers such as diethyl ether or tetrahydrofuran.

In another general process, (B), a compound of general formula (I) may be prepared by reaction of a compound of formula (V) :



(V)

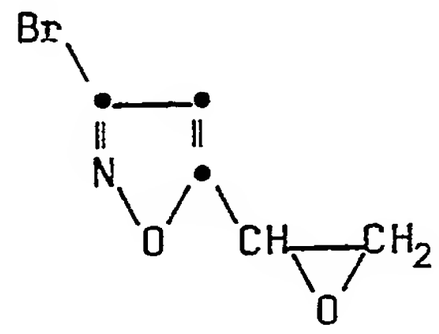
(wherein R^5 is a hydrogen atom or a protecting group and Hal represents a halogen atom, e.g. bromine) with an amine of general formula (VI) :



(VI)

followed where necessary by removal of any protecting groups. The reaction is preferably effected in the presence of a suitable acid scavenger, such as those described above. The reaction is conveniently effected in a solvent such as an alcohol, e.g. methanol or ethanol.

In a third process, (C), a compound of general formula (I) may be obtained by reaction of an amine of general formula (VI) with a compound of formula (VII)



(VII)

In the preparation of both intermediates and end-products the final step in the reaction sequence may be the removal of a protecting group(s). The protecting groups may be selected from conventional protecting groups as described for example in "Protective Groups in Organic Synthesis", by Theodora Greene (John Wiley and Sons Inc., 1981).

Intermediates of formulae (II), (V) and (VII) are either known compounds or may be prepared by methods analogous to those described for the preparation of known compounds.

Suitable methods for preparing intermediates of formulae (III), (IV) and (VI) are described in UK Patent Specifications Nos. 2140800A and 2159151A and in the exemplification included hereinafter.

In the general processes described above, the compound of formula (I) obtained may be in the form of a salt, conveniently in the form of a physiologically acceptable salt. Where desired, such salts may be converted to the corresponding free bases using conventional methods.

Physiologically acceptable salts of the compounds of general formula (I) may be prepared by reacting a compound of general formula

(I) with an appropriate acid or base in the presence of a suitable solvent such as acetonitrile, acetone, chloroform, ethyl acetate or an alcohol, e.g. methanol, ethanol or isopropanol.

Physiologically acceptable salts may also be prepared from other salts, including other physiologically acceptable salts, of the compounds of general formula (I), using conventional methods.

When a specific enantiomer of a compound of general formula (I) is required, this may be obtained by resolution of a corresponding racemate of a compound of general formula (I) using conventional methods.

Thus, in one example an appropriate optically active acid may be used to form salts with the racemate of a compound of general formula (I). The resulting mixture of isomeric salts may be separated for example by fractional crystallisation, into the diastereoisomeric salts from which the required enantiomer of a compound of general formula (I) may be isolated by conversion into the required free base.

Alternatively, enantiomers of a compound of general formula (I) may be synthesised from the appropriate optically active intermediates using any of the general processes described herein.

Specific diastereoisomers of a compound of formula (I) may be obtained by conventional methods for example, by synthesis from an appropriate asymmetric starting material using any of the processes described herein, or by conversion of a mixture of isomers of a compound of general formula (I) into appropriate diastereoisomeric derivatives e.g. salts which then can be separated by conventional means e.g. by fractional crystallisation.

The following non-limiting examples illustrate the invention. Temperatures are in ^{0}C. "Dried" refers to drying using magnesium sulphate or sodium sulphate. Thin layer chromatography (t.l.c.) was carried out on silica and flash column chromatography (FCC) on silica (Merck (RTm) 9385). The following solvent systems may be used : System A - toluene:ethanol:triethylamine; System B - toluene:ethanol:0.88 ammonia.

Example 1

3-Bromo-α-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-5-isoxazolemethanol

A solution of 1-(3-bromo-isoxazol-5-yl)-2-bromotethanol (1.80g), 6-(4-phenylbutoxy)hexanamine (3.31g) and diisopropylethylamine (1.72g) in ethanol (18ml) was stirred at reflux under nitrogen for 22h. The solvent was evaporated and the residue purified by FCC eluting with System A (98:2:1) to give a brown oil. Trituration with hexane gave the title compound as a fawn solid (850mg), m.p. 41°.

Analysis Found C,58.0; H,7.3; N,6.3; Br,18.0;

$C_{21}H_{31}BrN_2O_3$ requires C,57.9; H,7.3; N,6.2; Br,17.8%

Example 2

3-Bromo-α-[[[6-[[6-(2-pyridinyl)hexyl]oxy]hexyl]amino]methyl]-5-isoxazolemethanol

(i) 6-[[6-(2-Pyridinyl)hexyl]oxy]hexanamine

A solution of N-[6-[[6-(2-pyridinyl)hexyl]oxy]hexyl] benzenemethanamine (0.09g) in ethanol (40ml) was hydrogenated over pre-reduced 10% palladium on charcoal catalyst (50% aqueous paste, 524mg). After 24h hydrochloric acid (10N in ethanol, 25ml) was added and hydrogenation continued for 24h. The catalyst was removed by filtration and the filtrate evaporated to a yellow oil which was partitioned between ethyl acetate (75ml) and 8% sodium bicarbonate solution (50ml). The organic phase was dried and evaporated. Purification of the residue by FCC eluting with System B (90:10:1) gave 6-[[6-(2-pyridinyl)hexyl]oxy]hexanamine (0.34g), t.l.c. (System B, 90:10:1) Rf 0.10.

(ii) 3-Bromo-α-[[[6-[[6-(2-pyridinyl)hexyl]oxy]hexyl]amino]methyl]-5-isoxazolemethanol

A solution of 2-bromo-1-(3-bromo-5-isoxazolyl)ethanol (215mg), 6-[[6-(2-pyridinyl)hexyl]oxy]hexanamine (0.34g) and N,N-diisopropylethylamine (0.10g) in ethanol (10ml) was heated at reflux under nitrogen for 4h. Solvent was removed from the cooled

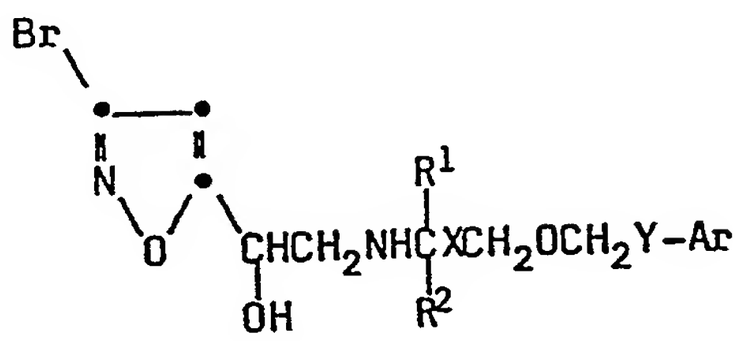
reaction mixture and the residue purified by FCC eluting with System A (95:5:1) to give the title compound (100mg), t.l.c. (System B, 80:20:1) Rf 0.53.

Analysis Found C,56.9; H,7.3; N,8.2;

$C_{22}H_{34}BrN_3O_3$ requires C,56.4; H,7.3; N,9.0%

CLAIMS:

1. Compounds of general formula (I)



(I)

wherein

R^1 and R^2 each independently represents a hydrogen atom or a C_{1-3}alkyl group with the proviso that the sum total of carbon atoms in R^1 and R^2 is not more than 4;

X represents a direct bond or a C_{1-7}alkylene, C_{2-7}alkenylene or C_{2-7}alkynylene group and Y represents a direct bond or a C_{1-6}alkylene, C_{2-6}alkenylene or C_{2-6}alkynylene group with the proviso that the sum total of carbon atoms in X and Y is not more than 10;

Ar represents a monocyclic aryl group selected from phenyl or pyridyl, wherein the phenyl group may be unsubstituted or substituted or by one or more substituents selected from halogen atoms, C_{1-4}alkyl, C_{1-4}alkoxy or hydroxy groups, or by an alkylenedioxy group of formula $-O(CH_2)_pO-$ where p is 1 or 2 and the pyridyl group may be unsubstituted or substituted by one or more substituents selected from halogen atoms, C_{1-4}alkyl, C_{1-4}alkoxy or hydroxy groups,
and physiologically acceptable salts thereof.

2. Compounds according to claim 1, wherein, in the general formula (I), the sum total of carbon atoms in claims X and Y is 4 to 10 inclusive.

3. Compounds according to claim 2, wherein, in the

general formula (I), R^1 and R^2 each represents a hydrogen atom.

4. Compounds according to claim 1, wherein, in the general formula (I), R^1 and R^2 each represents a hydrogen atom and Ar represents an unsubstituted phenyl or pyridyl group.

5. Compounds according to claim 1, selected from 3-bromo- α-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-5-isoxazolemethanol,
3-bromo- α-[[[6-[[6-(2-pyridinyl)hexyl]oxy]hexyl]amino]methyl]-5-isoxazolemethanol,
and physiologically acceptable salts thereof.

6. A pharmaceutical composition comprising, as active ingredient, a compound of general formula (I) as defined in claim 1 or a physiologically acceptable salt thereof together with one or more physiologically acceptable carriers therefor.

7. A pharmaceutical composition according to claim 6, formulated for administration by inhalation or insufflation.

8. A pharmceutical composition according to claim 7, formulated in unit dosage form containing 0.005 mg to 20 mg active ingredient.

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